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The role of Tc-99m polyclonal human immunoglobulin G scintigraphy in Graves' ophthalmopathy

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Objective: The aim of this study was to clarify whether Tc-99m HIG (Polyclonal Human Immunoglobulin G) can image and determine the severity of orbital involvement in patients with Graves' ophthalmopathy. ***Materials and Methods:*** Twenty-six patients between 19 and 56 years old with Graves' ophthalmopathy were examined. All patients received approximately 370 MBq Tc-99m HIG by i.v. injection. Planar and SPECT examination were performed 4 hours after the injection. Visual and semiquantitative evaluations were performed for both orbits by two independent observers, ***Results:*** Clinically active ophthalmopathy patients had noticeably increased orbital accumulation of Tc-99m HIG. In patients with inactive disease, and 14 of 19 had no uptake, whereas 5 patients had orbital radioactivity accumulation. The duration of Graves' ophthalmopathy did not correlate with the presence of active ophthalmopathy and Tc-99m HIG grade. There was no correlation between clinical classification and clinical activity (r = 278). There was a good correlation between clinical activity and the radioactivity grade with r = 0.666 (p = 0.01). The clinical classification closely correlated with Tc-99m HIG grade (r = 0.423, p = 0.05). ***Conclusion:*** Tc-99m HIG scan can clearly identified clinically active patients, and subclinicial inflammation can be shown by this scintigraphic evaluation. The current preliminary results suggested that Tc-99m HIG SPECT might be useful for the assessment of disease activity in Graves' ophthalmopathy.

Key words: Tc-99m human immunoglobulin G, Graves' ophthalmopathy, radionuclide imaging

INTRODUCTION

GRAVES' DISEASE is associated with a distinct eye disease, Graves' ophthalmopathy (GO). It seems to be an autoimmune disorder, primarily affecting the orbital fat and extraoccular muscles. GO is present in approximately 50% of patients but is usually transient. Clinically severe ophthalmopathy affects 5–10% of Graves disease patients.[1]

Exophthalmos is a characteristic finding in thyroid eye disease, occurring in 34 to 93% of patients. Enlargement of extraoccular muscle, increased orbital fat volume and orbital soft tissue inflammation could account for the proptosis. Abnormalities of eye motility are common. Optic nerve involvement, exposure keratitis may occur in patients with thyroid eye disease. The lacrimal gland may show evidence of mild to moderate inflammation. Patients with thyroid eye disease often complain of excessive lacrimation, a gritty sensation, discomfort and photophobia.[2–5] These symptoms and signs are related to the classical sign of inflammation.

A variety of immunologic changes have been demonstrated in the etiopathogenesis of Graves' ophthalmopathy. There is a lymphocytic infiltration of orbital tissue. The exact nature of the disorder is not clear.[6–8]

Two stages in the development of the disease are distinguished: active and inactive stages. Assessment of the activity of Graves' ophthalmopathy is important because of the need to choose an effective treatment modality. Active eye disease is likely to respond to immunosuppressive therapy with steroids or radiotherapy, whereas surgery is the first choice for inactive disease. In the majority of patients it is difficult to assess the disease

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activity clinically.[9–11] The gold standard is biopsy of the extraoccular muscles. But it is not a feasible method because of the involved risk. Therefore, imaging methods have been proposed for assessing the disease activity. CT is a valuable tool to evaluate the ophthalmopathy. This scan may also demonstrate muscle involvement in patients who otherwise have no clinical evidence of myopathy. But it cannot differentiate edema from fibrosis.[12,13] MRI can clearly delineate the findings of interest. The obvious limitations include the high cost and long scanning time involved. There are no clear advantages of MRI over CT in the clinical management of patients with thyroid ophthalmopathy.[14–16]

Octreotide scanning has been demonstrated as a semiobjective tool in evaluating ophthalmopathy, but some limitations restrict the widespread use of this method. These are high cost and a high radiation burden. Also some orbital diseases such as meningioma, sarcoidosis and Wegner's disease may cause false positive octreoscan findings.[17–21]

Tc-99m HIG is used for detecting infection and inflammation. The advantages of labeling with Tc-99m are short life, low radiation burden and low cost. In this study we evaluated the potential role of orbital polyclonal human immunoglobulin G uptake to determine the severity of the orbital inflammation in patients with Graves' ophthalmopathy.[22,23]

MATERIALS AND METHODS

Twenty-six patients (22 women and 4 men) with Graves' disease were included in the study and informed consent was obtained from all of them. The mean age of these patients was 38.15 ± 9.29 years with a range of 19–56 years. The duration of Graves' ophthalmopathy was 7.61 ± 4.77 months (range 1–24 months). All patients were taking antithyroid medications and 21 of them were hyperthyroid and 5 were euthyroid at imaging time. The diagnosis of Graves' disease was based on conventional clinical and laboratory criteria, which included high serum thyroid hormone levels, undetectable TSH values and diffuse enlargement of the thyroid gland. Ophthalmopathy was evaluated by physical examination and ophthalmometry. Ophthalmic examination included measurement of visual acuity, color vision, papillary function, evaluation of the eyelids, extraoccular muscle movements and biomicroscopic and fundus examinations. The degree of proptosis was measured with a Hertel exophthalmometer. The classification of eye changes in Graves' disease was made according to the scheme

Table 1 Data for all patients

Patient no.	age	sex	TFT	time (months)	Hertel R/L (mm)	Tc-99m HIG grade	clinical activity	clinical class
1	39	F	2	2	22/23	2	0	3
2	50	F	2	3	15/18	0	1	0
3	40	F	2	3	20/20	2	1	1
4	28	F	1	10	22/23	0	0	3
5	46	F	2	6	22/24	3	1	3
6	34	F	2	5	18/16	0	0	1
7	28	M	2	8	21/23	2	1	3
8	52	F	2	5	21/18	3	1	3
9	56	F	1	5	15/17	0	0	3
10	43	F	2	5	18/17	0	0	0
11	32	F	2	4	15/16	0	0	1
12	39	F	1	8	14/15	1	0	1
13	24	F	2	6	16/17	0	0	0
14	38	F	1	8	18/20	2	1	1
15	32	M	2	4	20/20	0	0	1
16	32	F	2	12	16/15	0	0	0
17	49	F	2	9	19/20	1	0	1
18	41	M	2	9	21/21	0	0	1
19	19	F	2	8	22/19	3	1	2
20	53	M	2	6	21/20	0	0	2
21	29	F	2	24	15/17	0	0	1
22	34	F	2	1	14/16	2	0	1
23	32	F	2	8	20/21	1	0	1
24	42	F	2	12	22/22	0	0	2
25	38	F	1	15	14/15	0	0	2
26	42	F	2	12	22/23	0	0	2

M: male, F: female, TFT (1: euthyroid, 2: hyperthyroid), time: duration of ophthalmopathy, clinical activity (0: inactive, 1: active)

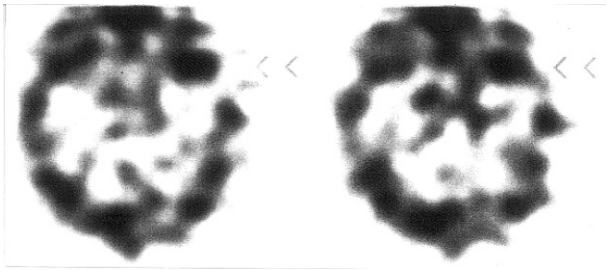

Fig. 1 Positive Tc-99m HIG orbital scintigraphy in patient with active Graves' ophthalmopathy showing radioactivity accumulation in the involved left orbit.

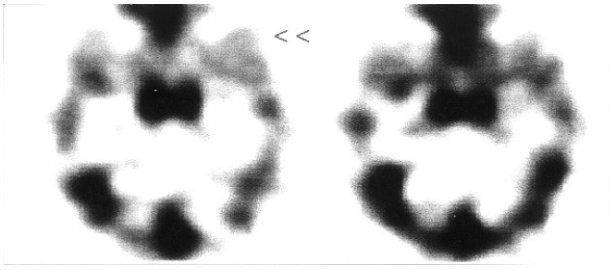

Fig. 2 There is no abnormal accumulation of Tc-99m HIG in patients with inactive orbitopathy.

proposed by a committee of the International Thyroid Associations. Abridged classifications of eye changes are summarized as follows: class 0: no signs or symptoms; class I: only signs, no symptoms (sign limited to upper eyelid retraction and stare, with or without lid lag and proptosis); class II: soft tissue involvement (symptoms and signs); class III: proptosis; class IV: extraoccular muscle involvement; class V: corneal involvement; class VI: sight loss (optic nerve involvement).[24,25]

Disease activity was assessed by the presence of acute inflammatory signs: spontaneous retrobulber pain, pain on eye movement, eyelid erythema, conjunctival injection, chemosis, swelling of the caruncle, and eyelid edema or fullness. Full description of the evaluation can be found in references 24 and 25. In all patients the disease was ophthalmologically monitored for 6 months.

A commercially available kit of HIG (Mallinckrodt Petene, The Netherlands) was labeled with 740 MBq Tc-99m. Thirty minutes after incubation and 370 MBq Tc-99m HIG was injected via an antecubital vein. After 4 hours, imaging was started. Static images of both eyes were taken with an Elscint SPX gamma camera equipped with a low energy, high resolution collimator in a 256 × 256 matrix size for 10 minutes. Tomographic imaging was then done in a 64 × 64 matrix, 25 seconds per frame with 6 angles over 360 degrees.

Visual and semi-quantitative analysis of all data were performed by two independent observers. Transverse SPECT images were reconstructed, and optimal orbital images on transaxial and coronal slices were selected. Semiquantitative evaluation was made by scoring the degree of radioactivity uptake in both eyes. A four point score was used to grade the intensity of uptake (0 = no uptake, 1 = slightly increased uptake from the background, 2 = moderate uptake, less than the nose, 3 = strong uptake, equal to or more than the nose).

Table 2 Clinically activity and Tc-99m HIG grade in all patients

	Tc-99m HIG grade			
	0	1	2	3
Clinical active (n = 7)	1	–	3	3
Clinical inactive (n = 19)	14	3	2	–

Table 3 Clinical class and HIG grade in patients

		Clinical class				
		0	**1**	**2**	**3**	
Tc-99m HIG grade	**0**	4	5	4	2	15
	1	–	3	–	–	3
	2	–	3	–	2	5
	3	–	–	1	2	3
						n = 26

Statistics

The Wilcoxon test was applied to compare the values. Probability values < 0.05 were considered significant. Correlations among various parameters were calculated by means of Spearman's test.

RESULTS

Tc-99m HIG uptake was seen in 11 of 26 patients, 13 of 52 orbits. Two patients who showed signs of bilaterally symmetrical orbital Tc-99m HIG uptake had clinically active disease. Data for all patients are summarized in Table 1. Clinically 7 patients were active and 19 were inactive. Six patients, who have active ophthalmopathy, had radioactivity (Fig. 1) but only one active patient had no uptake. Although there was no uptake in 14 of 19 patients who are inactive (Fig. 2), 5 patients (3 patients with grade I and 2 patients with grade 2) had uptake. In all clinically active patients, Tc-99m HIG uptake was grade 2 or higher (Table 2). Comparison of the clinical classes and Tc-99m HIG grades is summarized in Table 3.

The duration of Graves' ophthalmopathy did not show a correlation with the presence of active ophthalmopathy and Tc-99m HIG grade. The correlation between thyroid function and the Tc-99m HIG grade was not significant. Three of 5 euthyroid patients has no orbital Tc-99m HIG accumulation and also 11 of 19 hyperthyroid patients had no uptake. Among the patients with Tc-99m HIG uptake, no significant difference was detected between euthyroid

and hyperthyroid patients.

There was no correlation between the clinical classification and clinical activity (r = 278). The clinical classification showed a close correlation with the Tc-99m HIG grade (r = 0.423, p = 0.05). The correlation between clinical activity and the Tc-99m HIG grade was found to be significant (r = 0.666, p = 0.01).

DISCUSSION

In this prospective study, the patients who have Graves' ophthalmopathy were evaluated for orbital accumulation of Tc-99m HIG at different stages of the disease. We found a striking difference in orbital accumulation of radioactivity between patients with active and inactive disease. In Graves' ophthalmopathy, orbital accumulation of Tc-99m HIG is most probably due to the increased vascular permeability and accumulation and retention of macromolecules in the expanded extracellular fluid in the inflammatory tissue.[22] We suggest that Tc-99m HIG accumulation can cause inflammation more directly than Indium-111-DTPA-Octreotide, which binds *in vivo* to the cell membrane of activated lymphocytes expressing somatostatin receptors in retrobulbar tissue.

The first orbital octreotide scans for Graves' disease were reported by Postema et al.[21] Results of octreotide studies in patients with Graves' orbitopathy correlate closely with the clinical activity score.[15–21] Postema et al. and Moncayo et al. reported in patients with Graves' ophthalmopathy a positive correlation between the clinical activity score and In-111 octreotide uptake.[16,21] These studies demonstrated that orbital radioactivity uptake is able to determine the activity of the disease, giving a high positive scan in the active disease and a low positive or negative scan in the late phase of the disease.[20] We used a semi-quantitative scoring system and a relationship between the clinical activity and orbital Tc-99m HIG accumulation was noted. In the present prospective study, although performed in only a small number of patients, the findings suggested that Tc-99m HIG can be seen as a parameter of disease activity.

Periorbital swelling and other signs of ocular inflammation are seen to correlate with extraocular muscle volume on a CT scan. Also CT imaging of Graves' ophthalmopathy showed bilateral involvement in patients with apparent unilateral disease on clinical examination or muscle involvement in patients who otherwise have no clinical evidence of myopathy.

Nevertheless, superior soft tissue differentiation on MRI and no ionizing radiation and possibility of multiple sequences compared with CT scans has led to the employment of MRI for Graves' ophthalmopathy. Although conventional MRI is the ideal for discerning soft tissue because of its hydrogen content, it is unable to distinguish fat from water-containing tissue. Bailey et al. showed reduced muscle elasticity in the late phase and muscle stretching in the active phase of the disease. They showed that the STIR (Short Tau Inversion Recovery) sequence and cine MRI techniques could give an assessment of the level of active inflammation in the muscles and be able to detected subclinical disease. Their results demonstrate that the distinction between the two stages is not sufficient on clinical examination, and MRI also could help to detect subclinical disease.[26] Salvi et al. examined patients with upper eyelid retraction in the absence of other evidence of ophthalmopathy. They showed the involvement of eye muscles in 43% of patients by means of orbital imaging, and serum antibodies reactive with eye muscle membrane antigens were present in 96% of patients. Their results suggested that some patients with only inflammation of the eyelid muscles may be an isolated feature of ophthalmopathy and it reflects the only sign of a subclinical eye disease.[27]

Our results show that the presence of Tc-99m HIG accumulation in clinically inactive patients may be the result of existing subclinical inflammation. A relatively lower Tc-99m HIG grade in these patients than in active patients also may indicate the presence of an existing low grade inflammation.

Durak et al. using Tc-99m HIG in Graves' ophthalmopathy reported a "subclinical inflammation" in clinically inactive patients with radioactivity.[28] In Durak's article, sixteen patients with clinically inactive and seven patients with active disease were evaluated. They did not show a close correlation between the clinical classification and Tc-99m HIG grade, but we found a close correlation between these two parameters. This may be due to the different properties of patients or subjectivity in clinical classification. They showed a correlation between the duration of ophthalmopathy and Tc-99m HIG uptake, but no significant correlation between these parameters occurred in our study. This discordance may be related to differences in the duration of the disease in the patients selected for each study.

We concluded that patients with highly active eye disease can be clearly identified both clinically and scintigraphically. In patients with negative or intermediate clinical activity, a positive scan can identify a number of patients with active disease. At the time if a biopsy were taken it would be possible to evaluate clinical activity more objectively. The results of the present study demonstrated that Tc-99m HIG can be a useful method to determine disease activity in Graves' ophthalmopathy. Tc-99m HIG uptake in inactive groups suggested that this method could detect subclinic orbital inflammation.

Results are promising but larger, prospective, randomized studies are needed to establish the role of Tc-99m HIG in Graves' orbitopathy.

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